REMARKS

Status of Claims

Claims 1-30 are pending. Claims 1-9 and 20-27 have been rejected. Claims 10-19 and 28-30 stand withdrawn. Claims 1, 5, and 20 have been amended. Support for claim amendments can be found in paragraphs 0005, 0043, 0049, 0054, and 0075 of the subject specification. Applicants respectfully assert that no new matter has been added.

Claims 3, 4, and 22 have been canceled without prejudice or disclaimer. In making this cancellation without prejudice, Applicants reserve all rights in these claims to file divisional and/or continuation patent applications.

Remarks to the Abstract

In the Office Action, the Examiner objected to the Abstract because it allegedly does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). Applicants herein submit an amendment requested entry of the abstract into the specification after the claims. Applicants therefore request withdrawal of the objection.

Restriction/ Election Requirement

In the office action, the Examiner alleged that the claims are not linked by a special technical feature that makes a contribution over US Patent 5,628,994 and US Patent 5,861,163. The Examiner further alleged that Applicants' traversal on the grounds that the two references do not describe a method for enhancing immunogenicity was not persuasive, because US Patent 5,628,994 at paragraph 15 states that the serial passaged strain "does not revert to toxigenicity" and functioned as a "vaccine strain" and therefore served to enhance the immune response to the Vibrio cholera strain. The Examiner further alleged that US Patent 5,861,163, at Brief Summary paragraph 2, found that the isolated Fisher-Devlin immunotype is a vaccine strain that is attenuated but immunogenic, and induced an immune response to the bacterial strain. As such, the Examiner made the Restriction/Election Requirement final.

Applicants disagree. Although the vaccine strains in US Patent No. 5,861,163 and US Patent No. 5,628,994 may retain some immunogenicity, neither US Patent No. 5,861,163 nor

US Patent No. 5,628,994 describe using passaging as a method to enhance immunogenicity. Instead, US Patent No. 5,861,163 (column 4, lines 62-64) and US Patent No. 5,628,994 (column 11, lines 19-40) both describe using serial passaging through an animal host to attenuate a bacterial strain. In addition, neither US Patent No. 5,861,163 nor US Patent No. 5,628,994 disclose a bacterial vaccine vector that expresses a heterologous antigen. Therefore, Applicants maintain that the subject claims are linked to form a single general inventive concept. Since the subject claims are linked to form a single general inventive concept, Applicants maintain that the restriction requirement is improper.

35 U.S.C. § 102 Rejections

In the office action, claims 1-3, and 9 were rejected under 35 USC 102(b) as allegedly being anticipated by Mora et al. (US Patent 3,328,252, 1967). The Examiner alleged that Mora et al. describe the passaging of Pasteurella-based vaccines through chickens, isolating the Pasteurella from chicken liver after it died from infection, and repeating the passaging through naïve chickens.

Applicants disagree. Mora et al. do not describe passaging a recombinant bacterial vaccine vector expressing a heterologous antigen, and certainly not a recombinant Listeria vaccine vector. Therefore, Mora does not anticipate the claims. Applicants therefore request withdrawal of the rejection.

In the office action, claims 1, 3, 7, and 9 were rejected under 35 USC 102(b) as allegedly being anticipated by Mankoski et al., (J. Med. Microbiol, Vol. 48 (1999) pages 395-399). The Examiner alleged that Mankoski et al. describe the passaging of *Heliobacter pylori*-based vaccines through gnotobiotic piglets, isolating the *Heliobacter pylori* from piglets 28 days after inoculation, and repeating the passaging resulting in a greater colonization efficiency in subsequent infections.

Applicants disagree. Mankoski et al. do not describe passaging a recombinant bacterial vaccine vector expressing a heterologous antigen, and certainly not a recombinant Listeria vaccine vector. Therefore, Mankoski does not anticipate the claims. Applicants therefore request withdrawal of the rejection.

In the office action, claims 1-9, and 20-27 were rejected under 35 USC 102(b) as allegedly being anticipated by Frankel et al. (US Patent 6,099,848). The Examiner alleged that Frankel et al. describe passaging of an auxotrophic attenuated mutant Listeria that is capable, when exposed to required nutrients, of generating CTL responses and protective immunity against wild-type Listeria infection through a host, where the vector passes to splenocytes, which are then harvested for CTL analysis. The Examiner further alleged that passaging was repeated when two splenocyte samples were taken from the same animal; and when mice were boosted with a second inoculation; and that maximum bacterial load was demonstrated in that 100-fold fewer bacteria were detected in the spleens of mutant-infected compared with wild-type-infected mice.

Applicants disagree. Frankel does not describe the repeated passaging of a Listeria through a host in order to enhance the immunogenicity of the Listeria. In the section of Frankel et al. cited by the Examiner (col. 16, lines 9-19), Frankel describes a boost with a second inoculation of fresh bacteria, not with the harvested bacterial vector, as claimed. In addition, the collection of two splenocyte samples from the same animal described in col. 16 of Frankel is an *in vitro* method of expanding/stimulating the splenocytes for a specific CTL response (in which the first population of splenocytes is used as the source of T cells, the second population of splenocytes is treated with LLO and is used as the source of APCs, and the first and second splenocyte populations are mixed and tested for APC stimulation of T cells) and not a method of passaging a bacterial vector, as alleged by the Examiner. Thus, Frankel et al. describes neither repeated administration nor repeated harvesting of the bacterial vaccine vector, as claimed.

The Examiner also alleged that maximum bacterial load was demonstrated in that 100-fold fewer bacteria were detected in the spleens of mutant-infected compared with wild-type-infected mice (col. 19-20). Applicants disagree. Frankel compared the number of splenic bacteria in mice vaccinated with mutant and wild-type bacteria, but have no description of any determination of maximum bacterial load. Additionally, determining a maximum bacterial load where the number of bacteria harvested are compared to the number of bacteria harvested from the previous passage and the number of bacteria harvested from the following passage, as described in paragraph 55 of the subject specification, requires repeated administration, passaging, and harvesting of the bacterial vaccine vector, which was not demonstrated in

Frankel et al, as described above. Therefore, Frankel does not anticipate the claims and Applicants request withdrawal of the rejection.

In the office action, claims 1-9 and 20-27 were rejected under 35 USC 102(a) as allegedly being anticipated by WO 01/25399 A2. WO 01/25399 describes using tumor-targeted bacteria expressing a reporter protein to image tumors. The Examiner alleged that WO 01/25399 describe the passaging of *Salmonella, Listeria, Shigella*-based vaccines through a host, where the vector passes to the liver or tumor, which are then biopsied for a vector which is super-infective and tumor-specific.

Applicants disagree. Contrary to the Examiner's assertion, the passaging of the bacteria is not repeated as there is only one administration of the bacteria (pages 56-57, referenced by the Examiner, describes a one time collection of bacteria from various organs 5 days after Salmonella injection and 23 hours after administration of the FIAU marker). Further, the description in WO 01/25399 of using a biopsy of tumor cells in a selection assay for isolating a vector which is super-infective and tumor-specific (page 15, lines 26-27) describes *in vitro* testing of various vectors rather than repeated passaging of vectors through a host.

In addition, the Examiner alleged that pages 56-57 describe that a maximum bacterial load of 10^9 for tumor and 10^6 for liver was reached. Applicants disagree. Pages 56-57 describe bacterial cfu/g tissue after a single bacterial administration, but do not describe maximum bacterial load where the number of bacteria harvested are compared to the number of bacteria harvested from the previous passage and the number of bacteria harvested from the following passage to determine maximum bacterial load, as described in paragraph 55 of the subject specification. Thus, the WO 01/25399 reference does not recite every element of the claims and therefore does not anticipate them. Applicants therefore request withdrawal of the rejection.

In the office action, claims 1-3, and 7-9 were rejected under 35 USC 102(a) as allegedly being anticipated by Kleanthous et al., Vaccine, Vol. 19 (2001) pages 4883-4895. The Examiner alleged that Kleanthous et al. describe the passaging of *Heliobacter pylori*-based vaccines through mice, isolation of stomach tissue to evaluate *H. pylori* infection, and

repetition of the *in vivo* adaptation process until no further increase was observed in the level of gastric colonization.

Applicants disagree. Kleanthous et al. do not describe passaging a recombinant bacterial vaccine vector expressing a heterologous antigen, and certainly not a recombinant Listeria vaccine vector. Therefore, Kleanthous does not anticipate the claims. Applicants therefore request withdrawal of the rejection.

In view of the foregoing amendments and remarks, Applicants assert that the pending claims are allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

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